

REMARKS

Applicants respectfully request reconsideration of the present application.

CLAIMS STATUS

Applicants have canceled claim 26, without prejudice or disclaimer. Applicants reserve the right to file one or more continuing applications directed to the canceled subject matter in one or more continuing applications.

After the amendment, pending claims include a) examined claims 11-14, 17-18, 21-25 and 50-52 and b) withdrawn claims 15-16, 19-20 and 27-49.

MARCH 10, 2010 INTERVIEW

Applicants thank Examiners Isaac Shomer, Jeff Lundgren and Brian Gulledge for the interview, the substance of which is incorporated into the present response.

CLAIM REJECTIONS UNDER 35 U.S.C. § 112, ¶ 1

Claim 26 stands rejected as failing to comply with the written description requirement. Applicants believe that the revised claim set obviates the rejection.

CLAIM REJECTIONS UNDER 35 U.S.C. § 103(a)

Claims 11-13, 17-18 and 21-25 stand rejected as obvious over Mihalko et al. (U.S. Patent No. 5,340,587) in view of Webb et al. (U.S. Patent No. 5,814,335) in view of Hunt et al. (Am. J. Respir Crit Care Med 2000; 161:694-699). Applicants respectfully traverse.

Applicants respectfully submit that the PTO failed to establish a *prima facie* case of obviousness at least for the following reasons.

1) The PTO's conclusion regarding the motivation for combining references is based on impermissible conclusory statements

In the Office Action dated December 17, 2009, the PTO did not alter its statement of the rejection. Thus, Applicants address the rejection as formulated in the Office Action dated July 22, 2009.

On page 8 of the July 22<sup>nd</sup> Office Action, the PTO acknowledges that Mihalko does not teach all the elements of the claimed method by stating “Mihalko does not teach that the liposome comprises sphingomyelin”. To remedy the admitted deficiency of Mihalko, the PTO relies on Webb and Hunt. The PTO asserts in a sentence bridging pages 8 and 9 of the July 22<sup>nd</sup> Office Action that one would have been motivated to combine Mihalko with Webb and Hunt “because as taught by Webb, sphingomyelin increases the hydrolysis stability of cholesterol containing liposomes to acid hydrolysis; and further, as taught by Hunt et al. components of the lung afflicted with asthma are more acidic than those of healthy lung.”

Applicants submit that the PTO failed to establish a *prima facie* case of obviousness at least because the above cited reasoning for combining Mihalko with Webb and Hunt is a conclusory statement, which lacks articulated reasoning with rational underpinning. In this regard, Applicants bring the PTO's attention to *KSR International Co. v. Teleflex Inc.*, 550 U.S.\_, 82 USPQ2d 1385 (2007), where the Supreme Court emphasized that the analysis supporting a rejection under 35 U.S.C. §103(a) should be made explicit (even if the motivation supporting a combination of references is not expressly present in the references). The Supreme Court also stated, quoting *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006), that “[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning the legal conclusion of obviousness.” Furthermore, *KSR* acknowledged that some areas of technology, which are very unpredictable systems (certainly the case with pharmaceutical formulations), will often be unobvious in view of the absence of a reasonable expectation of success that two or more references can be combined to achieve a particular result discovered by an applicant.

The above cited justification for combining Mihalko with Webb and Hunt lacks articulated reasoning with rational underpinning and thus, is a conclusory statement because

the PTO fails to provide an explanation why one of ordinary would be seeking to improve hydrolysis stability of Mihalko's liposomes.

Applicants submit that Mihalko relates to a "method and system for treating bronchial constriction. The system includes a liposome composition containing a  $\beta_2$  -adrenoreceptor agonist in a liposome-entrapped form, and a device for aerosolizing a metered quantity of the composition," see Mihalko's abstract. In his disclosure, Mihalko emphasizes the importance of maintaining of the liposome integrity and size during the aerosolizing process. See, column 9, lines 31-35: "Because the aerosolization procedure may result in mechanical disruption of a liposome suspension, it may be important to establish that the nebulizing process does not significantly affect liposome integrity and size." Mihalko provides results of testing the integrity of his liposomes composition in his Example IV. Besides the integrity during the aerosolization, Mihalko also emphasizes the importance of liposome stability in fluorocarbon propellant, see e.g. Example V.

Hydrolysis stability to acid hydrolysis, which the PTO uses in its justification of the combination of Mihalko, Webb and Hunt, has nothing to do with either a) maintaining liposome integrity and size during the aerosolizing process or b) the liposome stability in fluorocarbon propellant, which are both important properties of his liposomes.

Applicants respectfully submit that the PTO's logic used in justification of combining Mihalko with Webb and Hunt is deficient because such logic can be used for justifying combining Mihalko with any reference (let's say reference A) that discloses a liposome that a) has one lipid component as one of Mihalko's liposomes and b) has some useful property because the PTO would have applied this logic and said that one ordinary skill in the art would modify Mihalko's liposomes to take advantage of the useful property of the reference A's liposome. Considering that any liposome can have at least one useful property, the PTO would have applied this erroneous logic against all the liposomes that contain at least one lipid component of Mihalko's liposome, and found them unpatentable for use in a method for pulmonary administration.

Applicants respectfully submit that, to provide the required articulated reasoning with rational underpinning for combining Mihalko with Webb and Hunt, the PTO needs to provide the following information:

i) why one of ordinary skill in the art would want to modify Mihalko's liposomes to obtain a liposome having a particular property, which is hydrolysis stability to acid hydrolysis, out of a very large, if not infinite, possible number of properties that liposomes can have;

ii) why one of ordinary skill would conclude that the PTO's proposed modification, which supposedly would lead to an increased hydrolysis stability to acid hydrolysis, would not make Mihalko's liposomes inoperative for their intended purpose, which is to be used for aerosolizing. In particular, the PTO has not shown why the proposed modification would not affect a) the liposomes' ability of maintaining of the integrity and size during the aerosolizing process or b) the liposome's stability in fluorocarbon propellant, which are both critical properties for Mihalko's liposomes.

Because the PTO did not provide such information, no *prima facie* case of obviousness is established.

In sum, at least for the reasons discussed above, Applicants request withdrawal of the rejection.

**B) The PTO's reasoning does not follow any of exemplary obviousness rationales from MPEP § 2143**

Applicants respectfully submit that during the March 10<sup>th</sup> interview, Examiner Jeff Lundgren suggested that Applicants present an argument that the PTO's reasoning does not follow any of exemplary rationales presented in MPEP § 2143, which are as follows:

"(A) Combining prior art elements according to known methods to yield predictable results;

(B) Simple substitution of one known element for another to obtain predictable results;

(C) Use of known technique to improve similar devices (methods, or products) in the same way;

(D) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results;

- (E) "Obvious to try" - choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success;
- (F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art;
- (G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention".

Applicants submit that the PTO's reasoning does not follow the rationale A at least because the PTO failed to articulate "a finding that one of ordinary skill in the art would have recognized that the results of the combination were predictable", which the Office personnel must articulate in order to base an obviousness rejection on such a rationale, see MPEP § 2143.A.

The PTO's reasoning does not follow the rationale B at least because the PTO failed to articulate "a finding that one of ordinary skill in the art could have substituted one known element for another, and the results of the substitution would have been predictable", which the Office personnel must articulate in order to base an obviousness rejection on such a rationale, see MPEP § 2143.B.

The PTO's reasoning does not follow the rationale C at least because the PTO failed to articulate "a finding that one of ordinary skill in the art could have applied the known "improvement" technique in the same way to the "base" device (method, or product) and the results would have been predictable to one of ordinary skill in the art", which the Office personnel must articulate in order to base an obviousness rejection on such a rationale, see MPEP § 2143.C.

The PTO's reasoning does not follow the rationale D at least because the PTO failed to articulate "a finding that one of ordinary skill in the art would have recognized that applying the known technique would have yielded predictable results and resulted in an

improved system”, which the Office personnel must articulate in order to base an obviousness rejection on such a rationale, see MPEP § 2143.D.

The PTO’s reasoning does follow the rationale E at least because the PTO failed to articulate any of the following: 1) “a finding that at the time of the invention, there had been a recognized problem or need in the art, which may include a design need or market pressure to solve a problem”, 2) “a finding that there had been a finite number of identified, predictable potential solutions to the recognized need or problem” and 3) “a finding that one of ordinary skill in the art could have pursued the known potential solutions with a reasonable expectation of success.” Applicants respectfully submit that the Office personnel must articulate each of the findings 1-3 in order to properly base rejection on the rationale E, see MPEP § 2143.E.

The PTO’s reasoning does not follow the rationale F at least because the PTO failed to articulate “a finding that one of ordinary skill in the art, in view of the identified design incentives or other market forces, could have implemented the claimed variation of the prior art, and the claimed variation would have been predictable to one of ordinary skill in the art;” which the Office personnel must articulate in order to base an obviousness rejection on such a rationale, see MPEP § 2143.F.

The PTO’s reasoning does not satisfy the rationale G at least because 1) the PTO failed to articulate the required finding regarding teaching, suggestion, or motivation to combine reference teachings and 2) the PTO failed to articulate a finding that there was reasonable expectation of success, see MPEP § 2143.G. The PTO’s reasoning regarding the motivation and the reasonable expectation of success cannot be considered the required articulated reasoning with rational underpinning because the PTO relies on conclusory and factually inaccurate statements, see section A above and section C below.

In sum, at least for the reasons discussed in this section, the PTO failed to establish a *prima facie* case of obviousness.

C) The PTO improperly evaluates facts established in Applicants' rebuttal against the conclusion of obviousness and relies on impermissible conclusory and factually inaccurate statements.

In the response filed October 22, 2009, Applicants provided three arguments. In the Office Action dated December 17, 2009, the PTO indicated that none of these three arguments is sufficient to overcome the rejection. Below Applicants provide their comments regarding the PTO's reasoning for disregarding each of the three October 22<sup>nd</sup> arguments.

1) The first argument presented on page 10 of the October 22<sup>nd</sup> response is based on the following facts: Mihalko's liposomes are multilamellar vesicle liposomes, while Webb's SM/Chol and DSPC/Chol liposomes are large unilamellar liposomes. Thus, even if for the argument's sake, the stability to acid hydrolysis would have been a desirable property for Mihalko's liposomes, one of ordinary skill in the art would not have concluded that suggested by the PTO inclusion of sphingomyelin in Mihalko's liposomes would predictably increase their stability to acid hydrolysis because of the different nature of a) Mihalko's liposomes and b) Webb's liposomes, for which the increase in stability to acid hydrolysis was supposedly demonstrated.

In the comments on page 5 of the Office Action, the PTO challenges the fact the Webb's teaching regarding the increase in stability to acid hydrolysis is limited to unilamellar liposomes by referring to column 2, lines 50-51 and column 5, lines 42-46, which, according to the PTO, provide the definitions of the term "liposomes" reading on both unilamellar and multilamellar liposomes. In view of these definitions, the PTO concludes that "one of ordinary skill in the art would have expected that sphingomyelin would have stabilized both unilamellar and multilamellar liposomes" and maintains the rejection."

In response, Applicants submit that Webb's Example 1, on which the PTO relies in its rejection, unambiguously relates to unilamellar liposomes. Applicants further submit that Webb's excerpts at column 2, lines 50-51 and column 5, lines 42-46 simply mention that liposomes may be unilamellar or multilamellar, however, these Webb's excerpts do not provide evidence that multilamellar liposomes' hydrolysis stability can be predicted from the hydrolysis stability of unilamellar liposomes. Without such evidence, the PTO's assertion

that “one of ordinary skill in the art would have expected that sphingomyelin would have stabilized both unilamellar and multilamellar liposomes” is a conclusory statement, which is not permissible in the obviousness analysis. In sum, at least for the reasons discussed in this section, the PTO failed to establish a *prima facie* case of obviousness. Accordingly, Applicants request withdrawal of the rejection.

2) The second argument presented on pages 10-11 of the October 22<sup>nd</sup> response is based on the fact that in his example 1, Webb compares the stability to acid hydrolysis of SM/Chol and DSPC/Chol, which are both two component liposomes. Thus, even if for the argument’s sake, the stability to acid hydrolysis would have been a desirable property for Mihalko’s liposomes, based on the Webb’s example 1, one of the ordinary skill in the art would rather be motivated to substitute PC lipid in Mihalko’s liposome with sphingomyelin instead of adding sphingomyelin to Mihalko’s liposome as suggested by the PTO. Because the substitution of PC lipid with sphingomyelin follows more logically from Webb’s example 1 than the PTO proposed addition of sphingomyelin, Webb teaches away from the PTO proposed modification of Mihalko’s liposome.

On pages 5-6, the PTO provides the following comment in response to the second argument:

“the examiner points to MPEP 2145(X)(D), which states that the nature of teaching away is highly relevant. Based on MPEP 2145(X)(D)(I), which states that "A known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use," the examiner does not understand a disclosure that SM/Chol is better than DSPC/Chol to constitute teaching away. While the examiner admits that, in the present case, Webb teaches that a Sphingomyelin/Cholesterol combination is superior to a phosphatidylcholine/Cholesterol combination in regard to acid hydrolysis, Webb does not expressly teach one of ordinary skill in the art against the combination of phosphatidylcholine and cholesterol. Hence, Webb does not teach away from a combination with Mihalko, and one of ordinary skill in the art would have been motivated to have combined sphingomyelin, as of Webb, with phosphatidylcholine and cholesterol, as of Mihalko.”

In response, Applicants submit whether or not the pattern qualifies as “teaching away” is irrelevant. The initial burden for establishing a *prima facie* case of obviousness is on the PTO. Thus, the PTO must provide an articulated reasoning with rational underpinning why one ordinary skill in the art would be motivated to add sphingomyelin in Mihalko’s liposomes, instead of substituting PC lipid in Mihalko’s liposomes with sphingomyelin, in view of the fact that the substitution follows more logically from the Webb’s example 1. Since the PTO did not provide such articulated reasoning with rational underpinning, the PTO’s conclusion that “one of ordinary skill in the art would have been motivated to have combined sphingomyelin, as of Webb, with phosphatidylcholine and cholesterol, as of Mihalko” is a conclusory statement, which is not permissible in the obviousness analysis. In sum, at least for the reasons discussed in this section, the PTO failed to establish a *prima facie* case of obviousness. Accordingly, Applicants request withdrawal of the rejection.

3) The third argument presented on page 11 of the October 22<sup>nd</sup> response is based on the fact that pH range in Webb’s test of acidic hydrolysis stability and Hunt’s pH values of deaerated exhaled airway condensate in patients with acute asthma do not overlap, so that even the lowest single patient pH value in Hunt is still outside Webb’s pH range. This lack of the overlap between Webb’s and Hunt’s pH values makes the PTO’s logic deficient.

On page 6 of the Office Action, in response to the Applicants’ third argument, the PTO provides the following commentary:

“Webb with Mihalko for the purpose of pulmonary administration as Webb teaches acid stability at pH values of 2 and 4, whereas Hunt teaches that affected lungs have a pH value of 5.23, the examiner disagrees with applicant’s contention that the lowest single patient pH value is “well above 4.0.” As of Hunt, page 695 left column Figure 1, the lowest pH value in the middle column of the figure entitled “Acute Asthma” appears to be well below 4.5 and almost 4.0. In fact, the median lung pH of those individuals with acute asthma appears to be lower than the mean as shown in Figure 1, due to three outlying values with a pH above 6. The examiner also notes Hunt, page 695 right column Figure 2, which shows two acute asthma patients with pH values starting close to 4. Hence, given the fact that the lung pH values of Hunt are acidic, and Webb teaches greater acid stability of liposomes comprising sphingomyelin, one of ordinary skill in the art would have reasonably expected that the addition of

sphingomyelin would have predictably rendered the liposomes of Mihalko in view of Webb to be more resistant to hydrolysis at the pH values of lungs affected by acute asthma.”

In response, Applicants submit no matter what words the PTO uses for characterizing Hunt’s lowest single patient pH value, this value is still unambiguously above 4 and, thus, outside Webb’s pH range. Furthermore, no matter what words the PTO uses for characterizing Hunt’s lowest single patient pH value, one of ordinary skill in the art would not be relying on a single patient value, such as Hunt’s lowest single patient pH value, for his/her conclusions because a single patient value is non-representative for the patient population at large. Instead, one of ordinary skill in the art would rely on a representative range defined by a mean value and a standard deviation. In Hunt, such a representative range is  $5.23 \pm 0.21$ , which is unambiguously outside Webb’s pH range. The PTO cannot arbitrarily pick and choose isolated parts of a reference and deviate from the logic that a person of ordinary skill would apply to this type of situation.

In sum, at least for the reasons discussed in this section, the PTO failed to establish a *prima facie* case of obviousness. Accordingly, Applicants request withdrawal of the rejection.

#### CONCLUSION

Applicants believe that the present application is in condition for allowance. Favorable reconsideration of the application is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing or a credit card payment form being unsigned, providing incorrect information resulting in a rejected credit card transaction, or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If

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any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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By 

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